PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X16250

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)
1 Nov 2005

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/038221	01.12.2004	12.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/138, A61K31/4468, A61K31/5375, A61K31/4704, A61K31/538, A61K31/5415, A61K31/40, A61K31/4025,

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III *Non-establishment of opinion with regard to novelty, inventive step and industrial applicability*
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/038221

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-3 (partially)

because:

☒ the said international application, or the said claims Nos. 1,3 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-3 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-3 (partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-3
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-3
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	2
	No:	Claims	1,3 (see separate sheet)

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2004/038221

Re Item III.

1. Claims 1 and 3 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. In reply to the objection to lack of unity, the applicant has paid one additional search fee for the invention of Group 4. The international search report has thus been established for the first and fourth inventions as identified in section IV below.

No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item IV.

The separate inventions/groups of inventions are:

1. Claims: 1-3 (partially)
Use of atomoxetine or a compound of formula (I) for treating hot flashes and vasomotor symptoms

2. Claims: 1-2 (partially)
Use of racemic reboxetine or (S,S) reboxetine for treating hot flashes and vasomotor symptoms

3. Claims: 1-2 (partially)
Use of a compound of formula (IA) for treating hot flashes and vasomotor symptoms

4. Claims: 1-2 (partially)
Use of a morpholine derivative of formula (IB),(IC),(IG),(IH) for treating hot flashes and vasomotor symptoms

5. Claims: 1-2 (partially)
Use of a compound of formula (ID) for treating hot flashes and vasomotor symptoms

6. Claims: 1-2 (partially)
Use of a compound of formula (IE) for treating hot flashes and vasomotor symptoms

7. Claims: 1-2 (partially)
Use of a compound of formula (IF) for treating hot flashes and vasomotor symptoms

8. Claims: 1-3 (partially)
Use of a selective norepinephrine reuptake inhibitor such as defined in claim 1 for treating impulse control disorders

9. Claims: 1-3 (partially)
Use of a selective norepinephrine reuptake inhibitor such as defined in claim 1 for treating personality change due to general medical condition

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

1.The first problem to be solved by the present invention is the treatment or prophylaxis of a number of diseases including
I) hot flashes or vasomotor symptoms,
the neurological disorders:
ii) impulse control disorders and
iii) personality change due to a general medical condition

The proposed solution is to use a selective norepinephrine reuptake inhibitor such as defined in the claims.

The use of the selective norepinephrine reuptake inhibitors of the present invention in therapy represents the technical features which may, a priori, unify the subjects mentioned above.

The selective norepinephrine reuptake inhibitors of the present invention, for example atomoxetine or a compound of formula (I), are known medicaments already used in the treatment of various neurological and mental disorders (see EP534756 and WO0240006).

Consequently, the idea to use the claimed selective norepinephrine reuptake inhibitor in medicine, including in neuropsychiatry, is known in the state of the art and cannot serve as a single general inventive concept linking the (further) uses I) to iii) which have no special technical features in common.

2. With regard to the first disease mentioned in the claims, the problem to be solved by the present invention is to provide a medicament for treating hot flashes or vasomotor symptoms.

The proposed solution is to use a selective norepinephrine reuptake inhibitor selected from:
1. atomoxetine or a compound of formula (I)
2. racemic reboxetine or (S,S) reboxetine
3. a compound of formula (IA)
4. a compound with a morpholine ring such as defined by formulae (IB),(IC),(IG),(IH)
5. a compound of formula (ID)
6. a compound of formula (IE)
7. a compound of formula (IF)

The selective norepinephrine reuptake inhibiting property, represents the technical feature which may, a priori, unify the different compounds 1 to 7.
It is clear from the description that by "selective" inhibitor it is meant a compound selective for the inhibition of norepinephrine reuptake relative to direct agonist or antagonist activity at other receptors. In this respect, selective dual inhibitors of serotonin and norepinephrine reuptake, such as those described in WO2004052858 and claimed as compounds of formula (IA), are contemplated by the present invention.

However, the use of selective dual serotonin and norepinephrine reuptake inhibitors for treating hot flashes or vasomotor symptoms has been already described in the state of the art.

WO02078691 discloses the use of the selective dual norepinephrine and serotonin reuptake inhibitor duloxetine for treating hot flashes.

XP4264310 and XP9026289 disclose the use of the selective dual serotonin and norepinephrine reuptake inhibitor venlafaxine for treating hot flashes.

Consequently, because selective norepinephrine reuptake inhibitors in the sense of the present invention have been already disclosed for the treatment of hot flashes in the state of the art (see the various references mentioned above), the selective norepinephrine reuptake inhibiting property (in the sense of the present invention) can no longer serve as a single general inventive concept linking the different compounds 1 to 7 which have no other special technical features in common.

Therefore, the use of the compounds 1 to 7 for treating hot flashes represents each a distinct invention, characterised by its own special technical feature, i.e. the structural feature of the compounds.

In the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed above. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art, i.e. the specific features of the individual compounds.

The present opinion has been established on the basis of the invention in respect of which a search has been carried out, in other words the first and fourth inventions (i.e. atomoxetine, a compound of formulae (I), IB, IC, IG, or IH in relation to the treatment of hot flashes and vasomotor symptoms).

Re Item V.

Reference is made to the following documents:

D1: WO 2004/035058 A (WYETH; DEECHER, DARLENE, COLEMAN; MERCHENTHALER, ISTVAN, JOSEPH; LEVEN) 29 April 2004 (2004-04-29)

D2: WO 2004/035036 A (WYETH; DEECHER, DARLENE, COLEMAN; MERCHENTHALER, ISTVAN, JOSEPH) 29 April 2004 (2004-04-29)

D3: WO 02/078691 A (ELI LILLY AND COMPANY; WALLACE, OWEN, BRENDAN; GARNETT, TIMOTHY, JOHN) 10 October 2002 (2002-10-10)

D4: LOPRINZI C L ET AL: "Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial" LANCET, vol. 356, no. 9247, 16 December 2000 (2000-12-16), pages 2059-2063, XP004264310 ISSN: 0140-6736

D5: QUELLA S K ET AL: "PILOT EVALUATION OF VENLAFAXINE FOR THE TREATMENT OF HOT FLASHES IN MEN UNDERGOING ANDROGEN ABLATION THERAPY FOR PROSTATE CANCER" JOURNAL OF UROLOGY, BALTIMORE, MD, US, vol. 162, no. 1, July 1999 (1999-07), pages 98-102, XP009026289 ISSN: 0022-5347

D6: WO 2005/047272 A (ELI LILLY AND COMPANY; CAMPBELL, GORDON, IAIN; CASES-THOMAS, MANUEL, J) 26 May 2005 (2005-05-26)

D7: WO 2005/023802 A (ELI LILLY AND COMPANY; CLARK, BARRY, PETER; GALLAGHER, PETER, THADDEUS) 17 March 2005 (2005-03-17)

D8: WO 03/037334 A (MERCK & CO., INC; ALVES, STEPHEN, E; HAMMOND, MILTON, L; WRIGHT, SAMUE) 8 May 2003 (2003-05-08)

1. The documents WO-A-2004/035058 (D1) and WO-A-2004/035036 (D2) which describe the use of atomoxetine for treating vasomotor symptoms and hot flashes are relevant for novelty for the subject-matter of claims 1-3.
The documents WO-A-2005/047272 (D6) and WO-A-2005/023802 (D7) which describe the use of a compound of formula IH (D6) or IG (D7) for treating vasomotor symptoms and hot flashes are relevant for novelty for the subject-matter of claims 1-2.

The priorities of the conflicting and the pending applications have however not been checked.

2. **Novelty**

2.1 The use of atomoxetine or a compound of formula (I) in the treatment of hot flashes and vasomotor symptoms has not been disclosed in the prior art at the priority date of the present application.
The subject-matter of claims 1-3, as far as it relates to invention 1, can thus be considered as new in the sense of Article 33(2) PCT.

2.2 The use of a morpholine derivative of formulae (IB),(IC),(IG),(IH) for treating hot flashes and vasomotor symptoms has not been disclosed in the prior art at the priority date of the present application.
The subject-matter of claims 1-2, as far as it relates to invention 4, can thus be considered as new in the sense of Article 33(2) PCT.

3. **Inventive step**

3.1 Invention 1

3.1.1 D3 to D5 disclose selective dual norepinephrine /serotonin reuptake inhibitors (duloxetine, venlafaxine) for treating hot flushes.
The problem to be solved, with respect to the disclosure of D3 to D5, appears to reside in the provision of an alternative medicament for treating hot flashes and vasomotor symptoms.

3.1.2 No indications were found that would have led the skilled person to choose atomoxetine or a compound of formula (I) in order to solve the problem posed.
Hot flashes are considered to be side-effect associated with older tricyclic antidepressant, known to be norepinephrine reuptake inhibitors similarly to atomoxetine (see D4).
An inventive step in the sense of Article 33(3) PCT is therefore acknowledged for invention 1.

3.2 Invention 4

3.2.1 Document D8 discloses the use of morpholine derivatives for treating hot flashes and vasomotor symptoms.
The problem to be solved, with respect to the disclosure of D8, appears to reside in the provision of an alternative morpholine compound for treating hot flashes and vasomotor symptoms.

3.2.2 No indications were found that would have led the skilled person to synthetise the compounds of formulae (IB),(IC),(IG),(IH) in order to solve the problem posed, so an inventive step in the sense of Article 33(3) PCT is acknowledged for invention 4.

4. Industrial applicability

4.1 There are no doubts about industrial applicability for the subject-matter of claim 2 (Art.33(4) PCT).

4.2 For the assessment of the present claims 1 and 3 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.